REMARKS

Claims 49, 56-63, 66-72 and 75-86 are pending and under examination in the above-identified application. Claim, 49, 56, 61, and 67-68 have been amended above. Support for the amendments can be found throughout the application as filed. Support for the amendment to claim 49 reciting an individual unaffected with colon, stomach or prostate cancer can be found, for example, in these claims as originally filed and at, for example, paragraphs 0017, 0161, 0169, 0280. Support for the amendment to claim 56 reciting healthy individual can be found at, for example, paragraph 0017. Support for the amendment to claim 61 can be found in cancelled claim 66. Claims 67 and 68 have been amended to correct their dependency from cancelled claim 66. Accordingly, the amendments do not introduce new matter and entry thereof is respectfully requested.

Rejections Under 35 U.S.C. § 112

Claims 49, 61-63, 66-71 and 85-86 stand rejected under 35 U.S.C. § 112, second paragraph. For claims 49 and 86 the Examiner alleges that the term "unaffected" is unclear. The term "encodes" also is alleged to be unclear because it refers to a nucleic acid sequence. For claims 61-63, 66-71 and 85-86 the Examiner alleges that the term "differential expression" is unclear apparently because it lacks a comparison.

While believed to be clear as written, claim 49 has been amended to explicitly state that the referenced individual is an individual unaffected with colon, stomach or prostate cancer. The claim also no longer recites a gene encoding a nucleic acid. With respect to claims 61 and its dependents, claim 61 has been amended to explicitly recite that the differential expression of the recited component is compared to a control. Applicants submit that these amendments render the rejections moot and their withdrawal is respectfully requested.

Claim 85 stands rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking written description. The Examiner alleges that the specification fails to provide a description of variants that are 95% or 98% identical to the claimed SEQ ID NOS because the specification fails to describe a representative number of species or recite any functional characteristics coupled with a known or disclosed correlation.

The written description test to determine entitlement to priority of an earlier filed application is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application. *Noelle v. Lederman*, 355 F.3d 1343, 1348 (Fed. Cir. 2004) (*citing Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). The specification must adequately describe the claimed invention so that one skilled in the art can recognize what is claimed. *Enzo Biochem, Inc., v. Gen-Probe Inc.*, 296 F.3d 1316, 1328 (Fed. Cir. 2002).

The specification provides sufficient support to satisfy the written description requirement under section 112, first paragraph. For example, variants and methods of making such variants are described at paragraphs 0116-0136. These paragraphs describe, for example, sequence variants encoded by the claimed SEQ ID NOS and that such variants can be made by, for example, site-specific mutagenesis of nucleotides in the DNA encoding the CA protein using techniques well known in the art to produce DNA encoding the variant (*Id.* at para. 0116). Therefore, by describing the variants of the polypeptides, and that they can be made by changing the encoding nucleic acid, the application describes variants of the encoding nucleic acid. The variants fall into substitutions, insertions and deletions that can be prepared from mutagenesis of the encoding nucleic acid. Moreover, as described therein, the variants typically exhibit the same qualitative biological activity as the naturally occurring sequence. Chart 1 further sets forth specific substitutions of amino acids that can be introduced by incorporated into the encoding SEQ ID NOS. This description of a number of variants of encoded by SEQ ID NOS:150, 152 and 154 is sufficient to satisfy the representative number of species articulated by the Examiner. Further, this description adequately describes the claimed invention such that one skilled in the art can recognize what is claimed. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claims 49, 56-63, 66-72 and 75-86 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking enablement. The Examiner asserts that in the absence of objective evidence one cannot determine whether the level of the claimed nucleic acids is different in colon cancer tissues as compared to non-cancerous tissues allegedly because the expression levels in cancer tissue is unpredictable. The Examiner further alleges that it is unclear what constitutes a normal tissue type, normal control, normal colon tissue or a control or whether the claimed differential

expression increases or decreases. It is further alleged that one cannot predict that any tissue type or any sample can be tested. The Examiner further alleges that the claimed sequences having 95% or 98% sequence identity would be unpredictable in the diagnosis of cancer. Finally, claim 60 stands rejected allegedly because the specification lacks guidance for how correlate the claimed differential expression with colon cancer risk. A number of references have been cited which allegedly support some of these points. The Office cites the seven factors of *In re Wands*, 858 F. 2d 731 (Fed. Cir. 1988), however, selectively addresses only a subset of these factors before concluding that undue experimentation is required to practice the full scope of the claimed invention. Applicants respectfully traverse the grounds of this rejection for the following reasons.

Initially, with respect to the assertion that the claims are unclear allegedly for use of the terms normal tissue type, normal control, normal colon tissue or a control, Applicants submit that this ground of rejection is moot in view of the amendments. With respect to the use of the term control in claim 61, Applicants respectfully submit that use of this term does not render the invention non-enabled for similar reasons to those provided in the analysis below.

Enablement does not require absolute predictability. Rather, requires that a person skilled in the art be able to practice the invention without undue experimentation. *In re Wands,* at 737 & 738. Factors to be considered in determining whether undue experimentation would be required to practice an invention included (1) the nature of the claimed invention, (2) the breadth of the claims, (3) the relative skill in the art, (4) the state of the prior art, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary to make or use the invention, (7) the amount of direction or guidance presented in the application, and (8) the predictability or unpredictability of the art. *Id.* No one factor is determinative, and the enablement requirement is met if a preponderance of the evidence indicates that it is more likely than not that any person skilled in the art at the time the application was filed could have practiced the claimed methods directed to diagnosing colon, stomach or prostate cancer by comparing the expression of the recited threonine endopeptidase encoding nucleic acids first in a test and control sample as claimed without undue experimentation. Applying the factors enumerated in *In re Wands* demonstrates that claims 49, 56-63, 66-72 and 75-86 are enabled and that undue experimentation would not be required to make and use the invention as claimed.

Factors 1 and 2: The nature of the claimed invention and breadth of the claims.

Claims 49, 56 and 72 are directed to methods for diagnosing colon, stomach or prostate cancer by determining the difference in expression of a threonine endopeptidase encoding nucleic acid (SEQ ID NOS:150, 152 and 154) in colon, stomach or prostate cancer tissue compared to non-cancerous colon, stomach or prostate tissue.. Claim 61 is similarly compares the difference in expression of proteasome component C7-I expression.

As taught by the specification, the use of oncogenic retroviruses —whose sequences insert into the genome of the host organism and result in cancer— has allowed the identification of host cancer related sequences such as threonine endopeptidase, defined as a cancer associated (CA) gene or nucleic acid sequence. See the specification at paragraphs 0027-0031, 0287 and Example 1, paragraph 298. In this regard, the specification teaches the use of three mammalian retroviurses (i.e., FeLV, MLV and MMTV) for tagging and identifying protooncogenes. See paragraph 0027, and paragraph 298. The specification describes that the integration of provirus affects the expression of host genes at or near the site of integration – a phenomenon known as retroviral insertional mutagenesis. See paragraph 0049. Possible changes in the expression of host cell genes due to insertional mutagenesis are taught to include: (i) increased expression of genes near the site of integration, (ii) decreased expression of genes due to functional inactivation caused by the integration, or (iii) expression of a mutated protein that has a different activity to the normal protein. See paragraph 49, lines 7-12.

The specification also teaches that differential expression of the CA genes such as threonine endopeptidase can be used for diagnosis of cancer or detection of cancer phenotype. See paragraph 0161. As will be discussed below, the specification further provides information about various means by which the differential expression of CA genes (including their mRNAs and proteins) can be determined. See Paragraphs 0074-0133. Thus, the present specification teaches that the differential expression of threonine endopeptidase encoding nucleic acids comprising SEQ ID NOs:150, 152 and 154 can be used as claimed for diagnosis of cancer.

Factors 3 and 4: The relative skill in the art and the state of the prior art.

The Office contends that the art of cancer diagnosis is unpredictable, and with respect to claim 60 that Tockman (Tockman, M.S. et al. Cancer Research, (SUppl.) 57:2711s-2718s, 1992)

teaches that research must validate the markers against acknowledged disease end points and confirm marker predictive value. Applicants respectfully traverse.

Applicants submit that the specification teaches one skilled in the art that the claimed sequences are sufficient to be predictive of colon, stomach or prostate cancer. As described above, the specification discloses that threonine endopeptidase encoding nucleic acid sequences SEQ ID NOS:150, 152 and 154 were discovered through the retroviral insertional mutagenesis as a marker for diagnosis of cancer. The specification teaches that the product of a CA gene such as threonine endopeptidase can be a marker for cancer diagnosis, when the gene expression is differentially altered in a tissue as compared to a control such as non-cancerous colon, stomach or prostate tissue or such tissue isolated from a healthy individual. See paragraphs 0017 and 161. The end point for which the threonine endopeptidase is to be a marker is measured, according to the specification, by differential expression that is defined and quantified in terms of up- or down-regulation. See paragraphs 0051 and 0052. The specification further establishes the range of threonine endopeptidase gene product variability in terms of, for example, sequence homology (of least 95% to threonine endopeptidase mRNA) or hybridization at stringent condition (of e.g., 60° C in 5X SSC). See paragraph 0065 and 0071. The specification further describes means for determining sequence homology in paragraphs 0066-0069 and provides detail disclosure for hybridization conditions in paragraphs 0071-0072. The specification also provides information about the biological samples which can be used for detecting the CA gene expression and diagnosing cancer. See paragraph 0278. The specification teaches that, for example, laser capture microdissection can be used to obtain samples from tumor and normal tissues. See paragraphs 0306 or 0316.

The present specification and the state of the prior art at the time the application was filed indicate that the relative skill in the art in relation to the subject matter to which the claimed invention pertains was high. At that time the application was filed, it was routine for a person skilled in the art to use recombinant DNA methods to determine the differential expression of, for example, threonine endopeptidase nucleic acids or products comprising or encoded by SEQ ID NOS:150, 152 or154 or a nucleic acid sequence with at least 95% homology with SEQ ID NOS:150, 152 or 154 or threonine endopeptidase protein in tissue samples.

As provided in the specification, it was also routine for one skilled in the art to be able to test threonine endopeptidase nucleic acids or their products for diagnosing cancer. Various means for diction of CA gene's nucleic acid product expression are disclosed in the specification at paragraphs 0074 to 0092. Various means for diction of CA gene's encoded protein expression are disclosed in the specification at paragraphs 0093-0133. Thus the specification not only taught that threonine endopeptidase nucleic acids and expression products can be used to diagnosing cancer; but it also provided detailed support for a skilled artisan to carry out the claimed methods for diagnosing cancer.

Factor 5: The presence of working examples.

The Office contends that in the absence of objective evidence one cannot determine whether the level of the claimed nucleic acids is different in colon cancer tissues as compared to non-cancerous tissues allegedly because the expression levels in cancer tissue is unpredictable and that one cannot predict that any tissue type or any sample can be tested. Applicants respectfully traverse.

The MPEP, Section 2164.02, states: "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation."

The specification in paragraph 0300, provides an example in which the RT-PCR method can be used for analysis of differentially expressed gene. See also Figures 2-4. In paragraph 0304, the specification provides an example of detection of elevated levels of cDNAs associated with cancer (e.g., threonine endopeptidase cDNA) using arrays. Methods for detection of CA sequences (e.g., threonine endopeptidase gene) in human cancer cells and tissues by way of hybridization are taught in Example 5, paragraph 0319. Furthermore, generation of antibodies against CA polypeptides (e.g., threonine endopeptidase polypeptide) is taught in Examples 7-8, paragraph 324-326. Various methods for detection of CA proteins (e.g., threonine endopeptidase protein) have also been taught in Examples 9-10, paragraphs 327-328.

The specification also teaches that "[c]omparing expression patterns of uncharacterized genes may provide clues to their function. High throughput analysis of expression of hundreds or

thousands of genes can help in (a) identification of complex genetic diseases, (b) analysis of differential gene expression over time, between tissues and disease states, and (c) drug discovery and toxicology studies. Increase or decrease in the levels of expression of certain genes correlate with cancer biology. For example, oncogenes are positive regulators of tumorigenesis, while tumor suppressor genes are negative regulators of tumorigenesis. (Marshall, Cell, 64: 313-326 (1991); Weinberg, Science, 254: 1138-1146 (1991))." See paragraph 0008. The specification also provides means for detection of cancer profile and correlating the expression levels of CA genes (e.g., threonine endopeptidase) to the cancer phenotype. See paragraphs 0161-0175.

Therefore, in view of the extensive teachings and exemplifications provided in the specification, a skilled artisan could have reasonably correlated the *in vitro* effects of the claimed methods to their *in vivo* utility in providing means for diagnosing cancers.

Factors 6 and 7: The quantity of experimentation necessary to make or use the invention and the amount of direction or guidance presented in the application.

The person of ordinary skill in the art would be able to practice the claimed invention following the guidance of the specification, using no more than routine experimentation. Threonine endopeptidase nucleic acids and techniques suitable for detecting their differential expression in a subject tissue and comparing it to a control such as non-cancerous colon, stomach or prostate tissure were known in the art at the time the application was filed. The specification further provides detail information for a skilled person to carry out the claimed method. See the information provided in Example 2 for analysis of quantitative RT-PCR: comparative C_T method; Example 3 for detection of elevated levels of cDNA associated with cancer using arrays; Example 4 for detection of CA-sequences in human cancer cells and tissues; Example 5 for detection of CA sequences in human cancer cells and tissues; Example 6 for expression of cloned polynucleotides in host cells; Example 7 for generation of antibodies against polypeptides; Example 8 for generation of monoclonal antibodies against a CA polypeptide; Example 9 for ELISA assay for detecting CA related antigens; Example 10 for identification and characterization of CA antigen on cancer cell surface; Example 13 for diagnostic imaging using CA specific antibodies; and Example 14 for immunohistochemical methods disclosed.

Thus, the specification teaches the person of skilled in the art that differential expression of CA genes (including threonine endopeptidase gene) and their products for diagnosing cancers are reliable and that detection of the differential expression leads to diagnosis of cancer. Accordingly, the specification provides ample guidance regarding the structure-function of threonine endopeptidase expression to enable any person skilled in the art to make or use the claimed methods without undue experimentation.

Factor 8: The predictability or unpredictability of the art.

The Office further contends that the claimed sequences having 95% or 98% sequence identity would be unpredictable in the diagnosis of cancer allegedly because the variants do not necessarily express at the same level as the corresponding wild type. Applicants respectfully traverse.

Applicants submit that the claims are directed to determining the difference in expression between the claimed sequences or those that are 95% or 98% identical to recited SEQ ID NOS. Accordingly, the level of expression is immaterial. Rather, it is the comparison as described previously above and taught throughout the application. Moreover, even if the Office's assertion applied to the claimed invention, Applicants respectfully point out that the patent statutes do not require absolute predictability, only that it would not require undue experimentation to make and use the claimed invention.

In view of the foregoing arguments, Applicant submit that claims 49, 56-63, 66-72 and 75-86 are enabled because, in view of state of art, teachings and exemplifications provided in the application, a person of ordinary skill in the art could make or use the claimed methods without undue experimentation. Accordingly, Applicant respectfully request withdrawal of this rejection.

Rejections Under 35 U.S.C. § 102

Claims 61-63, 66-67, 69, 83 and 86 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Tang et al. (US 2003/0219745). The Examiner alleges that SEQ ID NO:124 in Tang et al. is 98% similar to SEQ ID NO:154 recited in the subject application and that Tang et

al. describe at paragraph 211 that an increase in the level of SEQ ID NO:124 indicates ongoing cancer. Applicants respectfully traverse.

When lack of novelty is based on a printed publication that is asserted to describe the same invention, a finding of anticipation requires that the publication describe all of the elements of the claims. *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1349, 48 U.S.P.Q.2d 1225, (Fed. Cir. 1998) (quoting *Shearing v. Iolab Corp.*, 975 F.2d 1541, 1544-45, 24 U.S.P.Q.2d 1133, 1136 (Fed. Cir. 1992)). To establish a *prima facie* case of anticipation, the Examiner must show that the single reference cited as anticipatory art describes all the elements of the claimed invention.

Without conceding to the Examiner's assertion that the sequence in Tang et al. is the same or 98% similar to SEQ ID NO:154, Applicants respectfully point out that the cited support for SEQ ID NO:124 in Tang et al. fails to teach each and every element of the claim. Paragraph 211 of Tang et al. reads as follows:

> Polypeptides of the invention may be involved in cancer cell generation, proliferation or metastasis. Detection of the presence or amount of poly nucleotides or polypeptides of the invention may be useful for the diagnosis and/or prognosis of one or more types of cancer. For example, the presence or increased expression of a polynucleotide/polypeptide of the invention may indicate a hereditary risk of cancer, a precancerous condition, or an ongoing malignancy. Conversely, a defect in the gene or absence of the polypeptide may be associated with a cancer condition. Identification of single nucleotide polymorphisms associated with cancer or a predisposition to cancer may also be useful for diagnosis or prognosis.

Id. (emphasis added).

In contrast to the Examiner's assertion, the cited passage fails to teach that any of the polypeptides of the invention can be used for diagnosis of cancer nor does it specifically teach that SEQ ID NO:124 can be used for diagnosis. Rather, the cited paragraph speculates that some of the sequences might be amenable for use in diagnosis. Tang et al. describe 411 sequences and characterizes them as possibly being involved in cancer or possibly being useful for the diagnosis or prognosis of one or more types of cancer. Out of these 411 sequences Tang et al. fails to teach that SEQ ID NO:124 is involve in cancer or that it can be used for the diagnosis of cancer. Similarly, Tang et al. also does not teach that SEQ ID NO:124 is specifically involved with colon, stomach or prostate cancer or that it can be used for the diagnosis of colon, stomach or

prostate cancer. Absent such certainty, Tang et al. is speculative and fails to anticipate the invention as claimed.

CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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